Case Report

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Posted Date: 5 September 2025

doi: 10.20944/preprints202509.0567.v1

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Case Report

Hyperammonemia in Inherited Metabolic Diseases: A Case Report

Natalia A. Frankevich [1,*], Mzia I. Makeeva [1], Olga V. Mikhailova [1] and Vladimir E. Frankevich [1,2]

[1] National Medical Research Center for Obstetrics Gynecology and Perinatology Named After Academician V.I. Kulakov, Ministry of Healthcare of Russian Federation, 117997 Moscow, Russia

[2] Laboratory of Translational Medicine, Siberian State Medical University, 634050 Tomsk, Russia

* Correspondence: n_frankevich@oparina4.ru

Abstract

Certain hereditary or acquired conditions can elevate blood ammonia concentrations, causing severe damage to the central nervous system (CNS) due to ammonia's toxic effects on astrocytes. Consequently, patients with hyperammonemia exhibit potentially life-threatening neuropsychiatric symptoms, the severity of which depends on the magnitude and duration of ammonia exposure, as well as the stage of brain maturation. Inherited metabolic diseases caused by enzymatic defects that directly or indirectly impair the urea cycle are the leading cause of hyperammonemia in the neonatal period. The initial clinical manifestations of inborn errors of metabolism appear in the early neonatal period in nearly half of all cases, often with non-specific symptoms, making them challenging to recognize. Newborns suspected of having an inherited metabolic disease can be evaluated using biochemical tests; however, these are not always rapidly available. This underscores the critical need to expand newborn screening programs to facilitate earlier diagnosis and initiate specific treatment promptly, thereby reducing irreversible pathological processes that lead to disability and increased mortality. We present a case report of a full-term male infant diagnosed with a rare metabolic disorder caused by ornithine transcarbamylase deficiency.

Keywords: ammonia; hyperammonemia; urea cycle disorders; organic acidemias; ornithine transcarbamylase deficiency

1. Introduction and Clinical Significance

A number of congenital and acquired disorders can lead to hyperammonemia — an elevated level of ammonia in the blood. Ammonia is toxic to brain astrocytes, causing severe damage to the central nervous system (CNS). This manifests as life-threatening neuropsychiatric symptoms, the severity of which depends on the ammonia level, the duration of exposure, and brain maturity [1–3]. The primary cause of hyperammonemia in newborns is inherited metabolic diseases, such as urea cycle disorders, organic acidemias, and fatty acid oxidation disorders. The most severe and frequent cases are observed with the first two types of pathologies [4,5].

The challenge in diagnosing inherited metabolic disorders in newborns lies in the fact that nearly 50% of cases present with non-specific symptoms that can be easily mistaken for manifestations of more common conditions. Frequently, in remote regions, early diagnosis cannot be achieved in a timely manner, which leads to increased rates of disability and infant mortality [6,7].

The most significant clinical manifestation of urea cycle disorders (UCDs) is hyperammonemic crisis. UCDs are caused by mutations in the genes encoding the six enzymes or two transporters that facilitate the urea cycle — the primary pathway for ammonia detoxification in the liver and, to a lesser extent, in the kidneys [2].

There are two main clinical presentations. The early-onset form (in neonates) is characterized by a near-complete absence of enzyme activity, leading to the rapid development of toxic

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encephalopathy proportional to the ammonia level. The late-onset form exhibits residual enzyme activity, resulting in a milder disease course.

In newborns, the crisis typically develops after the first 24 hours of life, triggered by catabolic stress, protein load, or medication use. The consequences of hyperammonemia include persistent impairments in cognitive and behavioral development [2,6].

Treatment is aimed at reducing ammonia levels through medication and dietary management [8,9]. The high mortality rate in urea cycle disorders is primarily due to the development of encephalopathy. This process is initiated by the following cascade of events: ammonia crossing the blood-brain barrier, its detoxification in astrocytes via the synthesis of glutamine from ammonia and glutamate, the breakdown of protective mechanisms and subsequent accumulation of glutamate, neurotoxicity mediated by excessive glutamate acting on NMDA receptors (an ionotropic glutamate receptor that selectively binds N-methyl-D-aspartate), ultimately leading to damage and death of nerve cells [3,10].

Consequently, there is currently a pressing need to expand newborn screening panels using domestic test systems for the early detection of urea cycle disorders (UCDs) and the prompt initiation of specific treatment. This is crucial to reduce irreversible processes that lead to disability and increased mortality.

The aim of this study was to characterize a rare case of an inherited metabolic disease with neonatal manifestation that required hospitalization of the newborn in the Neonatal Intensive Care Unit (NICU) of the National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov.

2. Case Presentation

2.1. Patient History

Patient: Full-term newborn male, K., presenting with symptoms of hyperammonemia meeting the diagnostic criteria for an inherited metabolic disorder (as per the All-Russian Society of Pediatrics).

Diagnosis: Inherited metabolic disease (urea cycle disorder: ornithine transcarbamylase deficiency. Hyperammonemia). Neonatal seizures. Depression of the central nervous system (CNS) functions. Disseminated intravascular coagulation (gastric bleeding). Large for gestational age (LGA).

Laboratory and Instrumental Diagnostics:

Neurosonography and abdominal/renal ultrasound revealed no pathology. Echocardiography detected an aneurysm of the interatrial septum.

Complete blood count showed no signs of inflammation; the systemic inflammatory response marker, C-reactive protein (CRP), was within the normal age range. Urinalysis showed no inflammatory changes. Biochemical blood analysis revealed elevated activity of the following enzymes: gamma-glutamyl transferase, creatine phosphokinase, and creatinine levels up to 11.7 μmol/L.

The patient is a full-term male infant born to a 38-year-old woman from her first pregnancy, which was conceived naturally. The mother's obstetric and gynecological history was significant for primary infertility (2 years), external genital endometriosis, and uterine fibroids, which required surgical treatment (myomectomy without uterine cavity entry).

The mother had no significant chronic medical conditions. The first trimester of the current pregnancy was uneventful, and prenatal screening showed no abnormalities. The second half of the pregnancy was complicated by gestational diabetes mellitus (GDM), which required dietary management. On the eve of delivery, ultrasonography and external measurements indicated a large-for-gestational-age fetus, leading to a planned Cesarean delivery due to combined indications. The surgery and postpartum course were uneventful. The newborn's Apgar scores were 8 at 1 minute and 9 at 5 minutes, and no resuscitation measures were required. The infant was monitored in the

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well-baby nursery during the first day of life. He was put to the breast immediately after birth and was breastfed.

By the beginning of the second day of life, the infant developed respiratory distress and signs of hyperexcitability on neurological examination. Consequently, the patient was transferred to the NICU for further observation, diagnostic evaluation, and treatment. Upon admission to the NICU, non-invasive respiratory support with CPAP (Continuous Positive Airway Pressure) was initiated. At 20 hours of life, his condition deteriorated due to progressive neurological depression and the development of tonic seizures, necessitating endotracheal intubation and transition to invasive mechanical ventilation (IMV). Throughout the observation period, he remained hemodynamically stable and did not require cardiotonic support. On the second day of life, the infant developed gastric bleeding, prompting discontinuation of enteral nutrition and administration of fresh frozen plasma (FFP) transfusion. Instrumental investigations revealed no pathology of the cardiovascular or digestive systems.

Additional history obtained from the mother revealed significant family history: one maternal aunt died at 7 years of age from a metabolic disorder of unknown etiology, while another maternal aunt was found by exome sequencing to carry a pathogenic heterozygous mutation in the X-chromosomal ornithine transcarbamylase (OTC) gene, associated with ornithine transcarbamylase deficiency and hyperammonemia, which leads to one of the forms of hyperammonemia.

Given the neurological status upon admission to the NICU (presence of neurological depression), significant hyperlactatemia on the second day of life (up to 9.4 mmol/L), progression of pathological neurological symptoms with alternating periods of excitation and depression, the development of seizure syndrome, and the established family history, inherited metabolic disorders could not be ruled out. A consultation was held with the Head of the Pediatrics Department of the "Institute of Neonatology and Pediatrics" of the Center, Dr. Med. Sci., Professor A.V. Degtyareva.

Enteral feeding was discontinued, and intravenous fluid therapy was adjusted to exclude parenteral protein administration while increasing carbohydrate supplementation. Venous ammonia levels were monitored: 247 μmol/L upon admission, rising significantly to 622 μmol/L after 24 hours.

By the third day of life, the infant's condition deteriorated due to worsening pathological neurological symptoms, manifesting as progressive depression of CNS functions. Cerebral function monitoring (CFM) showed suppression of background bioelectrical activity with periodic epileptiform patterns, followed by the development of tonic flexion posturing in the upper and lower limbs and persistent tongue fibrillations. Anticonvulsant therapy (diazepam) was continued. Respiratory support (invasive mechanical ventilation) was maintained; the patient did not require supplemental oxygen and remained nil per os. Blood gas analysis revealed worsening metabolic acidosis. Table 1 presents a diagram visually illustrating the dynamics of the infant's condition and the rapid progression of the disease during the Center stay.

Table 1. Dynamics of the child's condition.

Assessment Category	**Day 1** **General Care Ward**	**Day 2** **NICU**	**Day 3** **NICU**
Clinical Status	Satisfactory (Enteral)	Severe (Parenteral)	Extremely Severe (Parenteral, Intubated)
Neurological Status	Age-appropriate	↓ Depression Agitation	↓↓↓ Worsening depression
Respiratory Support	Room air	CPAP	Invasive Mechanical Ventilation

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Assessment Category	Day 1 General Care Ward	Day 2 NICU	Day 3 NICU
Ammonia (μmol/L) *(Normal: 64–107)*	↑ 247	↑↑ 622	↑↑↑ **1058**
Lactate (mmol/L)	–	–	↑ 4.2 - 4.6
Outcome	–	–	**Transfer to Specialist Center**

Key: ↑ = Elevated, ↓ = Impaired/Diminished. Shading indicates worsening clinical state.

Given the distinctive family history, characteristic clinical presentation (development of progressive neurological symptoms in the infant at the beginning of the second day of life after an initial "honeymoon" period), and laboratory findings (rising hyperammonemia to 622 μmol/L in the absence of elevated inflammatory markers), the patient was diagnosed with: Inherited metabolic disorder: urea cycle disorder, ornithine transcarbamylase deficiency? Hyperammonemia.

Due to the necessity of specific therapy aimed at reducing blood ammonia concentration, including peritoneal/hemodialysis, the infant was transferred to a specialized department (Department for Rare Diseases) of the Morozovskaya Children's City Clinical Hospital (GBUZ DZM Morozovskaya DKB).

During follow-up, medical genetic counseling was performed, which confirmed the diagnosis of an inherited metabolic disorder. The boy's mother was also counseled by a geneticist at the stage of planning future pregnancies, and she was recommended to undergo medical genetic counseling.

3. Discussion

The body of scientific evidence indicates a serious prognosis for inherited metabolic diseases associated with hyperammonemia. The most severe outcomes in this group are associated with urea cycle disorders, which are characterized by rapid progression and high mortality risk in cases of delayed diagnosis. In this clinical case, the extensive experience of the Center and advanced laboratory capabilities enabled the rapid detection and monitoring of rising hyperammonemia levels. This, combined with the clinical manifestations and distinctive family history, facilitated the prompt diagnosis of a severe inherited disorder and transfer of the infant to a specialized unit for specific therapy. Unfortunately, such diagnostic resources are often unavailable in regional settings, or testing requires prohibitively long turnaround times, which can lead to severe neurological sequelae and early mortality.

Given that elevated ammonia concentrations in the brain exert direct neurotoxic effects, causing tissue damage and permanent neurological deficits, strict adherence to therapy is a determining factor in the outcomes of these diseases.

The diagnosis of congenital metabolic disorders leading to hyperammonemia involves the measurement of metabolites in biological fluids, and sometimes requires enzymatic assays and molecular tests that must be performed rapidly. Ammonia level is crucial for diagnosis and should be determined prior to these specialized laboratory investigations.

Ornithine transcarbamylase deficiency (OTCD) represents the most common form of inherited urea cycle disorders, with an estimated incidence of 1 in 56,500 live births [11,12] This disease is caused by partial or complete absence of ornithine transcarbamylase (OTC) enzyme activity, which catalyzes the condensation of carbamoyl phosphate and ornithine to form citrulline.

In contrast to other urea cycle disorders, OTCD is inherited in an X-linked manner. The neonatal form of the disease is characterized by the rapid development of life-threatening conditions,

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including cerebral edema, seizure syndrome, and coma, resulting in extremely high rates of mortality and disability. The most severe course is observed in male patients with a hemizygous status due to the presence of a single X chromosome. Phenotypic expression in heterozygous female carriers demonstrates significant clinical polymorphism—ranging from classical severe manifestations to completely asymptomatic carriage [11]. This clinical case vividly illustrates the broad spectrum of clinical manifestations of the disease: from the complete absence of symptoms in an asymptomatic carrier (the child's mother) to extremely severe manifestations presenting from the first days of life in her newborn.

Biochemical markers of OTCD include characteristic changes in the metabolic profile: hyperammonemia, elevated plasma concentrations of glutamine and alanine combined with reduced levels of arginine and citrulline, as well as increased urinary excretion of orotic acid. The encephalopathy resulting from hyperammonemia leads to irreversible impairment of motor and cognitive functions. Patients commonly exhibit delays in psychomotor development, attention deficit hyperactivity disorder (ADHD), and persistent cognitive deficits [10,11].

Given the hereditary nature of these disorders, the lack of readily available diagnostic capabilities, and the delays in initiating specific treatment—which lead to severe neurological consequences and infant mortality—it is imperative to implement detection of these diseases through newborn screening. This will help reduce disability and mortality in infants.

4. Conclusions

Hyperammonemia represents a life-threatening condition that requires immediate management of acute episodes, even prior to establishing a definitive diagnosis, to prevent irreversible neurological damage. Although clinical manifestations are often non-specific, inherited metabolic disease should be suspected in newborns who develop neurological symptoms following a period of relative well-being, however brief.

Timely and effective management of hyperammonemia plays a crucial role in determining prognosis and minimizes the risk of disabling complications. When hereditary metabolic pathology is suspected, basic biochemical investigation is essential. Expanding newborn screening programs and implementing rapid diagnostic protocols enable earlier initiation of specific treatment, which significantly reduces mortality rates and long-term complications.

Author Contributions: Conceptualization, N.A.F.. and V.E.F..; methodology, N.A.F. and M.I.M.; validation, N.A.F. and O.V.M.; investigation, M.I.M. and O.V.M.; resources, V.E.F.; data curation, N.A.F.; writing—original draft preparation, N.A.F. and O.V.M; writing—review and editing, N.A.F., M.I.M., O.V.M., and V.E.F.; visualization, N.A.F.; supervision, V.E.F; project administration, V.E.F.; funding acquisition, V.E.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the state assignment of the Ministry of Healthcare of the Russian Federation (Registration No 125050605833-4).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. According to current Russian regulations as well as the policies of our institution, ethical approval from an Institutional Review Board is not required for a case report, provided that the patient has given informed consent for publication. This is in line with the national guidelines and the position of the Russian Data Protection Authority, which does not mandate ethics committee approval for single-patient case reports that do not include sensitive personal data beyond what is necessary and where appropriate consent is obtained.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed at the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

 doi:10.20944/preprints202509.0567.v1

Abbreviations

The following abbreviations are used in this manuscript:

ADHD	Attention Deficit Hyperactivity Disorder
CFM	Cerebral Function Monitoring
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
CRP	C-Reactive Protein
FFP	Fresh Frozen Plasma
GDM	Gestational Diabetes Mellitus
IMV	Invasive Mechanical Ventilation
LGA	Large for Gestational Age
NICU	Neonatal Intensive Care Unit
NMRC OG&P	National Medical Research Center for Obstetrics, Gynecology and Perinatology
OTC	Ornithine Transcarbamylase
OTCD	Ornithine Transcarbamylase Deficiency
UCD	Urea Cycle Disorde

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